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# A Critique of a Controversial Study on THC Effects in Primates

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## Introduction

At this huge meeting, where over 25,000 neuroscientists from all over the world gathered to trade information on all facets of brain research, there appeared only one study on the effect of delta-9-tetrahydrocannabinol (THC) in primates. There were no studies in humans. Two other studies in rats or mice showed interaction of THC with nicotine and opiates, but these animals were given a THC-per-weight dose approximately 1000 times that of primates, so the models must be viewed with that massive dose in mind, and thus are not reviewed in this report.

The primate study, funded by the U.S. National Institute for Drug Abuse (NIDA) and carried out by S.R. Goldberg, P. Munzar, and G. Tandra, was entitled "Self administration behavior maintained by delta-9-tetrahydrocannabinol, the psychoactive ingredient of marijuana in squirrel monkeys." It should be noted that the lead author, Dr. Goldberg, works at the Preclinical Pharmacology Section of NIDA in Baltimore, MD. Dr. Goldberg was present at the report at a poster session presentation on Sunday, November 5, and responded to my questions and provided a copy of the poster.

*"a small number of squirrel monkeys ... were first taught to self-administer intravenous cocaine."*

## The Study

In essence, a small number of squirrel monkeys (the number is not specified in the poster, but 4 animals are identified in graph labels) were first taught to self-administer intravenous cocaine by pressing a lever when a light came on (a fixed-ratio reinforcement schedule). This step was necessary because numerous attempts over the past 30 years to get any animal to self-administer THC have been unsuccessful. Training occurred in one-hour experimental "sessions" conducted daily on weekdays. Once accustomed to getting the cocaine, this response was "extinct" by not giving the cocaine after the lever press until the monkeys only pressed the lever a tenth as much as when the cocaine was given. Just how long this extinction took is not reported, but it was more than 3 sessions, according to graphical data. Then THC doses reportedly comparable to that received by smoking a reasonable amount of marijuana (1 to 8 micrograms per kg, I.V.) were given in response to a lever press, using a second-order reinforcement protocol. The monkeys quickly learned over 1 to 3 sessions to press the lever to get this "reward." In short, they seemed to like the effects, at least up to a point. Careful observation of the graphical data indicated that up to 4 ug/kg per dose, the animals pressed the lever more frequently. At 8 ug/kg doses, however, there was a distinct and highly significant reduction in lever presses to the level of half that found with 4 ug/kg. No explanation was given for this finding, and it was not mentioned in the study results or conclusions. The experiment also included sessions after pre-administration of SR141716A, a drug which seems to block the effects of THC, but not cocaine. On this regimen, the monkeys reduced their lever pressings to the extinction point in three days, recovering the lever press frequency to THC 2 to 3 sessions after the blocking agent was stopped. No effect of SR141716A was seen in sessions where cocaine was the test drug.

## Official Study Conclusions

The six conclusions reached by the study authors were as follows:

- 1) "The active principle in cannabis, THC, possesses strong reinforcing properties in experimental animals, in this case, non-human primates, as it does in human subjects."
- 2) "The findings further suggest that marijuana has as much potential for abuse as other drugs of abuse, such as cocaine and heroin."
- 3) "The selective reduction of THC but not cocaine self-administration by SR141716A indicates that this abuse potential is likely mediated by cannabinoid CB1 receptors in the brain."
- 4) "THC self-administration by squirrel monkeys was obtained using a range of doses in agreement with the total intake and the single doses self-administered by humans smoking marijuana cigarettes."
- 5) "The recent discovery of new therapeutic actions of marijuana has increased public debate on the legalization of smoked marijuana as a medication. The present findings of persistent, reliable self-administration behavior with marijuana's psychoactive ingredient, THC, should help to better inform this debate."
- 6) "This methodology provides an exciting opportunity to study neuropharmacological mechanisms underlying marijuana abuse and to develop drugs possessing therapeutic efficacy similar to or better than marijuana or THC but lacking the potential for abuse."

## The Conclusions as Seen by This Observer (JSC)

The above six conclusions as rewritten after careful study of the poster:

- 1) Once cage-raised, chair-restrained squirrel monkeys are habituated to self-administering intravenous cocaine as a "drug of entry", they tend to self-administer intravenous THC under similar conditions. Any extension of this conclusion to non-primates, or other primates, including humans, cannot be made by this study.
- 2) No conclusion as to the abuse potential of THC in squirrel monkeys or any other species can be drawn from this limited study. However, the finding that higher doses of THC reduce the self-administration rate in these monkeys indicates that there is a self-limiting "ceiling" to the self-administration of THC in this species.
- 3) SR141716A blocks the self-administration of THC in

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squirrel monkeys previously habituated to cocaine self-administration. Where and how this action takes place cannot be drawn from this study.

- 4) Intravenous THC self-administration by squirrel monkeys habituated to cocaine seems to occur only at a dosage range similar to the dosage range of respiratory self-administration of THC-containing smoke in humans.
- 5) The present limited findings of self-administration behavior with marijuana's psychoactive ingredient, THC, may prove to be valuable concerning public debate on the legalization of smoked marijuana as a medication. But these findings should not be unduly extended or even be found to be reliable until verified in independent laboratory experiments.
- 6) This methodology may provide an opportunity to study neuropharmacological mechanisms underlying marijuana self-administration by cage-raised monkeys and to screen drugs possessing therapeutic efficacy similar to or better than marijuana or THC but lacking the potential for self-administration by these monkeys.

## Discussion

This particular study is important in that it shows how strongly the sponsor of a scientific study affects the conclusions drawn from the work. In this case, Drs. Goldberg, et. al, performed a fairly rigorous scientific investigation, then apparently embellished the report to satisfy NIDA official policy. This bias is shown from the first sentence of the poster, which reads: "Marijuana is among the most abused illicit drugs in the world." Note the NIDA-inspired keywords - "abused," "illicit," and even "drugs." The authors simply could not write "Marijuana is among the most used psychoactive agents in the world" without putting their funding, careers, and livelihood in jeopardy. This is the cloud under which NIDA scientists must function if they are to survive. When I brought this up to Dr. Goldberg at the meeting, he at first denied that he could lose his job because he was tenured. But he did not deny that he worked independently of outside influence. After all, tenure means little today when administrators can

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assign you to a small windowless office in the basement and deny funding for your work.

Accordingly, the authors' conclusions are grossly tainted by this bias, as exemplified by the two comparative sets of conclusions shown above. Extending the "strong reinforcing properties" of cannabis to humans in the first conclusion is an example. There weren't any humans in the study! How can this then be a scientific conclusion? What has been shown in

the study is that a handful of chronically bored and possibly depressed cage-raised and restrained squirrel monkeys that have been specially taught to self-administer IV cocaine will also self-administer IV THC. This is the first time any animal has been taught to self-administer THC under *any* conditions. To extend this very limited result to include human behavior is grossly unscientific.

Furthermore, any researcher worth his grant money should have noticed the ceiling effect of reasonable THC doses in these monkeys. These captive and drug-trained monkeys liked THC, but only in a very limited way. Why did they reduce lever pressing at the higher dose of THC? Were they “stoned” and passive or drifting off? This is not mentioned in the poster. Perhaps this is the well-known ceiling effect of THC (seen in humans) that was not recognized as a worthwhile finding, as it indicates that THC self-administration has intrinsic limits that are far short of the toxic dose of THC.

But why labor over the “NIDA-Speak” in the study poster at all? One seasoned neurophysiologist remarked that he always ignores the obvious propaganda-laced conclusions, and goes right to the graphs and technical data to find what really occurred in NIDA studies. That may be fine if one is a neuroscientist, but politicians may read only the conclusions and rush to legislate public policy with drastic results. Indeed, Dr. Goldberg proudly told me that the conclusions of this study had already been influential in the recent British debate in parliament where the conservatives had insisted on draconian penalties for simple marijuana possession. The “addictive” properties of THC shown by this study had been one of the main arguments for the increased penalties.

In conclusion, this interesting and provocative study includes some well carried out primate research into THC use, but the scientific data are sullied by untenable “conclusions” consisting almost entirely of NIDA propaganda. Discussion of this state of affairs brought out an appropriate quote from a Russian Neurophysiologist at the Meeting: “The American approach to the drug problem is like a doctor who treats a cough with a strong laxative. The treatment may stop the cough for a while, but it does nothing for the underlying problem.”

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## Response to Critique of THC Study

By Dr. Steven Goldberg  
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I do appreciate the opportunity to review the critique by Dr. Campbell. There are inaccuracies and problems of interpretation in the critique, which I should note. The major findings in this poster were published in a leading peer-reviewed journal, *Nature Neuroscience*, the month of the Neuroscience Meeting (2000, volume 3, pages 1073-1074). It was a press release by *Nature Neuroscience* about the article that resulted in public debate in Great Britain just before the Meeting.

As Dr. Campbell suggests, these findings should not be “unduly extended” and, of course, need to be replicated by independent laboratory experiments, but our research does provide preclinical evidence of what has long been clear from

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clinical experience, that marijuana has abuse potential like other abused drugs and is a potential medical problem. The principal guide for the medical community in diagnosing psychiatric disorders is the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-4, 2000) published by the American Psychiatric Association. It clearly describes marijuana (cannabis) as an abused drug capable of producing dependence and intoxication (pages 236 to 242). Marijuana is indeed illegal in the United States, Great Britain and much of the rest of the world. When I am writing about caffeine, I do refer to it being the most used psychoactive agent in the world, but marijuana is not caffeine and it is illegal.

Finally, the presence of a “ceiling effect” as the injection dose of THC was increased in our self-administration studies is exactly the same effect seen with other abused drugs such as cocaine or heroin under the same conditions. It is commonly referred to as an inverted u-shaped dose-response curve. However, the presence of an inverted u-shaped dose-response curve under controlled experimental conditions does not mean that a drug such as cocaine or heroine (or THC in marijuana) is free of toxicity and safe for human consumption.